REMARKS

1. Claims

The present claims are directed to second and higher level glycopeptide libraries. Such libraries can be obtained by steps which comprise random glycosylation of existing carbohydrate structures of a library comprising glycopeptides.

The "level" of a glycopeptide library indicates the number of rounds of glycosylation employed in synthesizing the library.

P9, L2-9 states

> A first level library of a desired glycopeptide is created by primary glycosylation of the peptide with a single glycosyl donor or a mixture of donors. Reaction of a core peptide with a glycosyl donor, or mixture of donors, results in a library of randomly glycosylated glycopeptides. A first level library... can form the basis for generating higher level libraries.

Thus, a first level library is the result of glycosylating unglycosylated peptides. A glycosyl donor can glycosylate such a peptide at any glycosylation site. For example, mono- and oligosaccharides can be N-linked to the peptide, by reaction with the NH_2 group on the side chain of Asn (or the NH_2-terminal of the peptide), or O-linked to the peptide, by reaction with the OH group on the side chain of Ser, Thr or hydroxylysine. P1, L21-28; P6, L14-20.

If the peptide were reacted with a single donor (i.e., random glycosylation were not employed), then the only way that a first level library could have the diversity implied by the term "library" would be if there were diversity in the amino acid sequence, e.g., by glycosylating a peptide library like that of P2, L9-30.

Random glycosylation is achieved by reacting the starting

peptide(s) with a mixture of different glycosyl donors, such as galactosamine, N-acelylgalactosamine, and sialyl. P8, L9-21.

What, then, is a second or higher level library? According to P9, L10-25,

> A second level library is created by reacting one or more first level libraries with one or more further glycosyl donors. Prior to further reaction, unreacted glycosylation sites on the peptides may be blocked, e.g., by acetylation, in order to prevent these glycoforms from being eliminated from the library by being converted into different glycoforms. Following purification, the protecting groups of the carbohydrate structures on the glycoforms are selectively removed to create additional glycosylation sites on the existing carbohydrate structures. Random glycosylation with these additional donors further extends existing carbohydrate structures, thereby to create more complex glycopeptide structures. Higher level libraries are similarly created by reacting one or more second level or higher libraries with one or more further glycosyl donors.

When a glycosyl donor is reacted with a glycopeptide of a first level library, in theory it can react either (1) with a glycosylation site on the side chain of an unglycosylated amino acid, or (2) with a glycosylation site on a carbohydrate structure of the first level glycopeptide. If, prior to this second glycosylation reaction, the unreacted glycosylation sites on the amino acids are blocked, then possibility (1) is eliminated, and the second glycosylation can only extend the existing carbohydrate structure.

In reciting that peptides are "randomly glycosylated", applicants indicate that the starting peptide(s) are given the opportunity to react with the members of a mixture of glycosyl

donors, and that some molecules are thus glycosylated. We do not mean to imply that every single peptide molecule must in fact be glycosylated; that would be contradictory to the teachings of P9, L12-13 to the effect that some glycosylation sites may remain unreacted.

Claim 32 has been rewritten to avoid product-by-process language, and to require O-linkage of the carbohydrate to the peptide scaffold.

New claim 47 recites that the peptide scaffolds are cyclic peptides.

New claim 48 recites that the peptide scaffold comprise at least one D-amino acid.

New claim 49 recites that the peptide scaffold comprises at least a four amino acid subsequence of the core protein of MUC1.

New claim 50 recites that one or more of the carbohydrate structures comprises sialic acid.

New claim 45 is a composite of the distinctive limitations of amended claim 32 and new claims 45-48, which are all dependent, through claim 46, on 45. However, if the Examiner would prefer, we can cancel 45-46 and rewrite 32, 45, 46, 47 and 48 as independent claims. While claim 45 says that the library comprises glycopeptides with the same scaffold, claim 46 insists that all of the peptides, including glycopeptides, have the same scaffold. Please note that the libraries can include an unglycosylated peptide corresponding to the original peptide scaffold(s). Please also note that it is possible to mix together libraries, each made from a single scaffold, to obtain a new library featuring several different scaffolds, which is why claim 45 is not limited to a single scaffold.

Method-of-use claim 38, as amended, requires only screening for target-binding (i.e., "antibody-like") activity.

Screening for biological activity has been moved to new claim 50, screening for immunostimulatory activity to new claim 51, and screening for competitive inhibition to new claims 52-53.

Table 1 (P. 10) sets forth the diversity of a first level library in which a single peptide scaffold, with 1-5 glycosylation sites, is randomly glycosylated with 1-5 different glycosylation donors, in such a manner that the degree of glycosylation of the peptides varies, from molecule to molecule, from 0 to 100%. Thus, with 5 glycosylation sites, as in SEQ ID NO:1, and a single glycosylation donor, the library has an overall diversity of 32, the library members consisting of one unglycosylated peptide, five singly glycosylated peptides, 10 doubly glycosylated peptides, 10 triply glycosylated peptides, five quadruply glycosylated peptides, and one quintuply glycosylated peptide. The library thereby consists of 31 glycopeptides and one unglycosylated peptide.

Claims 55-59 are based on Table 1, with 5 glycosylation sites and 1-5 carbohydrate structures. Note that peptides are considered "different" if they have different glycosylation patterns, even if they have the same amino acid sequence. Also, "glycopeptides" are a subset of "peptides".

The diversity of a second level library will be equal to that of the first level library if the same sugar is added to all existing carbohydrate structures. More often, different sugars will be added, randomly, so its diversity will be greater than that of the starting first level library.

Claim 60 is based on table 1 with 2 sites and 2 structures. This corresponds to the first level library #3 of p. 25. Claim 61 is based on second level library #7 at P27, L35, which is derived from first level library #3.

Claim 62 is based on claim 1, as amended, of 09/842,873.

Claim 63's four amino acid limitation is based on the

GSTA disclosure in Example 1.

Claims 64-65 refer to the peptide as being "derived" from a "cancer-associated mucin" (64) or from a MUC1 core protein (65). We interpret "derived" to allow the peptide to be a fragment of the core protein of the mucin (e.g., MUC1), since there is specific disclosure of two fragments of MUC1 (a 16 a.a. fragment at P11, L17-21, and a four amino acid fragment in Example 1 on p. 13). We also interpret "derived" as allowing replacement of L-amino acids with the corresponding D-amino acids, in accordance with the teachings of P6, L21-25, labeling of amino acids with UV-active or fluorescent labels per P6, L26-28, cyclization of the peptide per P6, L26, and lipidation per P6, L37-P7, L2. Naturally, it also allows for glycosylation.

Claims 66-69 and 72 are related to the above disclosures. Claims 70-71 are based on P5, L36-37.

Claims 73-74 refer to the component carbohydrate structure diversity, and are based on the number of different glycosyl donors in the reaction mixture, at least three (claim 73) or at least five (claim 74), per P8, L16, P9, L33. Claims 75-77 relate to the extent of the glycosylation. Claims 75 and 77 presuppose that all glycosylatable AAs are free, per P7, L4-5. Claim 76 formally describes the distribution of library members vis-a-vis degree of glycosylation which is inherent in the formula of P9, L29. See also P11, L21-34; P24, L2-12; P27, L17-P28, L9.

Claims 78-82 define, in various ways, the variation in glycosylation pattern among the glycopeptides of the library.

2. Prior Art Issues

Claims 32, 34-38 and 42-43 were rejected as anticipated by or obvious over Rao. Likewise claims 32 and 34-38 were rejected as anticipated by or obvious over (1) Vetter or (2)

Schleyer. Finally, claims 32-37 were rejected as anticipated by or obvious over Frische et al. (J. Pept. Sci. abstract).

2.1. Rao creates a glycopeptide library using fucose-serine building blocks. No amino acid other than serine is glycosylated, and no sugar other than fucose is disclosed. Thus, there is no randomness in Rao's glycosylation step. Rather, the randomness is in the amino acids to which the Fuc-Ser is attached.

The Examiner, in support of the argument that Rao teaches random reaction, refers us to Rao col. 21, lines 44-49:

> In a similar manner as shown in Example VII, other peptide derivatives containing (multiple) carbohydrate residues are prepared to mimic the binding of SLex to selectin binding sites. Carbohydrate residues include mannose, glucose, N-acetylglucosamine, N-acetylgalactosamine, galactose and sialic acid.

However, this passage is fairly read as teaching replacement of fucose with one other carbohydrate selected from the recited group, not reaction of the peptide with a mixture of all of the suggested carbohydrates. All discussions of randomization are in the context of the amino acid sequence, see, e.g., col. 8, lines 39-45.

The instant claims require a carbohydrate structure diversity which is manifestly absent from Rao. Rao does not obtain the "same library product", and does not suggest randomization of the carbohydrate content.

2.2. Vetter et al. (pp. 25-27) discloses the synthesis of glycoconjugate library of the form Ac-X-X-E(OAl)-X-P-resin, where Ac is acetyl, E is Glu, P is Pro, each X is randomly selected from a set of 18 side chain-protected AAs, and "OAl" is the allyl ester protecting group. First, a peptide library (diversity 18^4) was synthesized. Then it was converted into a

glycopeptide library by removing the allyl ester and replacing it randomly with one of a set of 17 glycosylamines (P26, L29-31); these were mono- or disaccharides.

Thus, Vetter randomly glycosylated a glycosylation site on a "platform" (peptide) to create a first level library of glycosylated platforms, per step (a) of claim 1.

In Vetter's application, the disclosed method is to make N-linked glycopeptide (glycoconjugates) libraries. The glycosylation acceptor (preferably a peptide), has a free carboxylic acid (-COOH) as a side chain. In a naturally occurring peptide, the amino acids with free carboxylic acid side chain functionalities are Asp and Glu. This glycosylation acceptor is pre-activated, i.e., the free -COOH side chain is converted into a reactive pentafluorophenyl (Pfp) ester. Then the glycosyl donor, a carbohydrate with an amine (-NH2) attached to the reducing carbon, i.e., a glycosylamine, is reacted with the activated ester to form an amide linkage between the carbohydrate and the carboxyl side chain of the peptide (i.e., carbohydrate-**N**H-CO-peptide).

The effect of the last step is to convert Asp (side chain $-CH_2COOH$) or Glu (side chain $-CH_2CH_2COOH$) into Asn (side chain $-CH_2CONH_2$) or Gln (side chain -CH2Ch2CONH2), respectively. Since the carbohydrate is then attached to the N of the resulting Asn or Gln, it is considered to be N-linked.

Vetter's glycosylation donors will not react with the hydroxy functions of Ser or Thr to form O-linked moieties; Vetter only generates N-linkages.

Claim 32, as amended, contemplates reaction of a peptide (the glycosylation acceptor) having at least one free hydroxyl group (i.e., an O-linkable glycosylation site) with a mixture of glycosylation donors, so that at least some of the peptides are O-glycosylated. That is, the result of the reaction is to form some glycopeptides in which the sugars are O-linked to

the core peptide. (If the peptide comprises amino acids with free amino groups, the donors can also react at these sites to form N-linked glycopeptides.) In either case, the amino acid sequence remains unaffected.

Our method and Vetter's produce different libraries. Thus, if the initial core peptide is VDTA, Vetter will obtain just VDTA or VN*TA (where * denotes glycosylation), while we obtain VNTA, VNT*A, VN*TA and VN*T*A.

If the core peptide were PDTRP (a Muc1 epitope), we would obtain PDTRP or PDT*RP, while Vetter would obtain PDTRP or PN*TRP.

If the core peptide were NQN[1], we obtain 8 different species (NQN, N*QN, NQ*N, NQN*, N*W*N, N*QN*, NQ*N*, and N*Q*N*). Vetter could make a library which contained N*Q*N*, but he would have to start with the core peptide DED, and he would then also obtain N*ED, DQ*D, DEN*, N*Q*D, N*EN*, and DQ*N*.

2.3. Claims 32-37 stand rejected as anticipated by or obvious over Frische et al. abstract (J. Peptide Sci.). In general, we think it inadvisable for the Office to cite abstracts; the entire article should be made of record. A copy of the article is enclosed.

Frische et al. studied the fragment 67-76 (VITAFNEGLK) of CBA/J mouse hemoglobin, which binds to CBA/J mouse MHC class II molecule E^k.

Frische et al. first synthesized the series of peptides #s28-67 set forth in Table 5. These peptides are single substitution mutants[2] which differ from the native fragment in

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[1] This core peptide is outside claim 32, but is cited to show how Vetter's chemistry results in N-linked glycopeptides with altered sequences. A core peptide like NQNT could generate a library within claim 32.

[2] Peptide #40 is actually the natural fragment.

that a single amino acid is replaced by Ser, Thr, glycosylated Ser or glycosylated Thr. The glycosylated AAs of Table 5 are all glycosylated with D-GalNAc. Frische systematically replaced each amino acid of the 10 a.a. fragment in this manner ("scanning mutagenesis"), thereby obtaining 40 different peptides, 20 of which were glycosylated.

Frische et al. discovered that the Hb (67-76) peptide became immunogenic when position 72 was Tn (i.e., D-GalNAc)-glycosylated.

Hence, Frische prepared a second series of 12 peptides, set forth in Table 6. The position 72 amino acid was Ser, Thr or Gln, and it was glycosylated with β-D-Gal, β-D-GalNAc, α-L-FUc, β-L-Fuc, β-D-GlcNAc, α-D-Man, α-D-Glc(1-4) β-D-Glc, α-D-Glc (1-4)α-D-Glc(1-4)-β-D-Glc, or α-D-GlcNAc. Only 12 of the possible combinations were explored. When position 72 was Ser or Thr, the carbohydrate was O-linked, and when position 72 was Asn, the carbohydrate was N-linked.

The Table 6 peptide series is not a library as each glycopeptide was individually synthesized on its own column of a 20 column manual synthesizer. There was no randomization because at no time was a mixture of glycosyl donors used as a reactant. Hence, there is no anticipation of the instant claims.

If Frische et al.'s peptides 68-79 were mixed togther, this could be considered a library, but it still would not anticipate because the library members would not have the same peptide scaffold. There would instead be three different scaffolds.

Frische et al. does not provide motivation to mix together only the glycopeptides which have the same core peptide sequence, such as his peptides #'s 68-71.

Frische is further distinguished by several dependent claims, e.g., claim 75, which requires that the peptide

scaffold comprise a plurality of glycosylation sites and that at least one of the molecules in the library be glycosylated at all of those sites.

3. Utility/Enablement (OA pp. 2-5)

The Examiner asserts that the library does not have a specific and well established utility, even as a "research tool", because

(1) libraries are not one of the "research tools" enumerated in MPEP 2107;

(2) since there is no claimed structure for the library, the library cannot be used for screening purposes.

(3) the issuance of patents on third party combinatorial libraries is irrelevant as each case must be judged omits own merits.

(4) the library is useful only to the extent that an individual compound in the library has the sought for binding activity.

We answer these points as follows:

(1) MPEP 2107 does not purport to provide an exhaustive list of "research tools". Moreover, it does list "screening assay". An assay is a method, not a "tool". So by reference to "screening assays", it really means assay kit components. A library could readily be a component of a screening assay kit, and indeed combinatorial libraries are sold as such.

(2) The synthesizer of a given library would know which peptide scaffold, was used, and which glycosylation sites were exposed to which glycosylation reagents. Thus, such user would know the "structure space" explored by the library.

Even a user who did not synthesize the library could analyze several members of the library and make deductions as to the nature of the peptide scaffolding and glycosyl donors

used.

If a library glycopeptide bound to a target, its structure could be determined without undue experimentation by mass spectrometry, as disclosed at P12, L17-19.

(3) The courts have given weight to third party patents when they occur in sufficient numbers to imply existence of a consensus in the art. The following cases illustrate the relevance of prior patents:

Ex parte Brian, 118 USPQ 242, 245, (POBA 1958) (past practice of office in accepting definiteness of "fingerprint" claims);

In re Chakrabary, 596 F.2d 952, 985-86 (CCPA 1979) (product claims reciting microorganisms previously treated as directed to statutory subject matter);

Andrew Corp. v. Gabriel Electronics, Inc., 6 USPQ 2010, 2012 (Fed. Cir. 1988) (term "substantially" is "ubiquitous" in patent claims and therefore considered definite);

In re Cortright, 49 USPQ2d 1464 (Fed. Cir. 1999) (Construction of "restore hair growth" for purpose of determining both §112 enablement and §101 utility; prior art references may be indicative of how a claim term will be interpreted by those of ordinary skill in the art);

Vitronics Corp. v. Conceptronic Inc., 39 USPQ2d 1573, 1578-9 (Fed. Cir. 1996) (prior art used to demonstrate how a disputed term is used by those skilled in the art, and indeed is more objective and reliable than post-litigation expert opinion testimony);

Pioneer Hi-Bred International v. J.E.M. Ag Supply Inc., 49 USPQ2d 1813, 1819 (N.D. Iowa 1998) (issuance of Boehm USP 2,048,056 in 1936 is evidence

that "in those instances where inventors showed they could define a reproducible plant meeting the limits of §112, plant patents were issued under §101".)

A large number of patents have issued with broad combinatorial compound library claims of some kind. In Appendix 1, we provide a sampling of these patents. This non-exhaustive listing is mainly of claims to combinatorial libraries of peptides, proteins, peptoids and polynucleotides, as the diversity of the library is more immediately apparent than is the case for a claim to, e.g., a benzodiazepine library. Clearly, the examiners of these patents thought that the claimed libraries had utility and were enabled for their full scope, even though they were not limited (as the present examiner proposes) to close analogues of a specific molecule already known to have a particular activity.

There are a far larger number of patents with broad claims to methods of making or using combinatorial libraries. (A few examples are given in Appendix 2.) The standard of enablement utility for product claims is no more stringent than that for method claims. The issuance of these patents implies that the libraries have utility, because a method of making or using a useless product would itself lack utility. They, too, must be deemed fully enabled, even though they are not limited to specific scaffolds.

(4) Actually, while it is certainly desirable that a library have a "hit", useful information is extracted even if there are no "hits". If, for example, MUC1 glycosylated with Tn and TF had no "hits", then the skilled worker would be discouraged from synthesizing and testing (1) the individual glycopeptides expected to be in the library, and (2) individual glycopeptides similar to those of (1) above. Thus, future testing could be rechanneled into more fruitful

directions. And it is much less trouble to combinatorially synthesize and screen a library of 10^6 glycopeptides than to process them individually.

3.1. The first enablement rejection (bottom of OA p. 5) is predicated on the alleged lack of 35 USC 101 utility and hence is overcome by the argument in the last section.

4. Enablement Issue

Another enablement rejection is stated at OA pp. 7-8.

The Examiner concedes that the specification is enabling for (1) generating a glycopeptide library using "mucin 1 (MUC1) as the core protein", and (2) screening that library for compounds with "inhibitory activity", but questions enablement for more broady claimed libraries.

The specification clearly contemplates use of platforms other than MUC1. Peptides, and in particular the core proteins of cancer associated mucins, are of particular interest (P1, L9-13). There is no reason to believe that other peptides would be more difficult to randomly glycosylate then would MUC1. Many different natural glycopeptides are known in the art. Of course, the starting peptide must feature at least one glycosylation site.

Platforms are discussed further at P5, L30-P7, L11. The specification says that the "platform" can be a peptide and, if so, that it may be linear or cyclic. It is also clear that the peptide may be composed of l- or d-amino acids. Reference is made to hydrophobic amino acids at P6, L35-37, and to glycosylatable amino acids at P1, L21-28.

Several specific platforms other than MUC1 are disclosed. The first is Tn antigen. Since Tn antigen is GalNAc-O-serine, the platform is just Ser per se. TF antigen has the same platform (P7, L30-34).

Another platform of interest is the one shown in Fig. 4.

This is a peptide with an unusual bridged structure. See also the peptoid (-CH_2CH_2- linkage) of Fig. 5. We also mention OSM and CA27.29 at P11, L11-14.

Please also see our discussion of Appendices 1 and 2 in the prior section. Claims were issued, hence deemed fully enabled, even though they were not limited to specific scaffolds.

5. Description Issues

5.1. The Examiner maintains description rejection "B" from pp. 5-6 of the office action of May 21, 2001:

> The specification fails to provide an adequate description of the components of a library that has competitive inhibitory, immunostimulatory or antibody activity. The specification provides a generalized statement as broad as the claimed invention. The components of the library are merely recited to be a glycopeptide without defining the structure. Without defining the structure, the glycopeptide comprises ever conceivable possible combinations of diverse structures defined only by the different opposite functions such as inhibition, immune stimulation or antibody activity.

The immediate office action (pp. 6-7) adds:

> Applicants argue that armed with applicants' disclosure of how to produce a combinatorial glycopeptide library, a skilled artisan readily could select platforms and carbohydrates to produce a library of compounds likely to contain some with of the recited activities.
>
> In response, applicants fail to specifically point out the relevant section applicants are relying on. Thus, it is not clear as to the method that a skilled artisan needs to employ to accomplish which of the different opposing

activities the library possesses.

If we understand this rejection correctly, the underlying reasoning is this:

(1) the disclosed activities ("competitive inhibitory, immunostimulatory or antibody activity" or "inhibition, immunostimulation or antibody activity") are "opposite", i.e., unlikely to be possessed by the same compound.

(2) the structures of the library members are defined only by a general compound class (glycopeptide) and a function, and, since the disclosed functions are "opposite", the encompassed structures are diverse.

When a claim is to an individual peptide, and the utility is dependent on the sequence, there is reason to say that "description" requires recitation of the sequence. However, the utility of a library is dependent on its diversity.

Claim 32 requires that for a given library, all of the (glyco)peptides have the same peptide scaffold. The only variation, consequently, is with regard to which carbohydrate structures are attached to that scaffold and where. Moreover, the choice of scaffold (core peptide) limits the possible location of the carbohydrate structures, as they must have been attached as a result of glycosylation of a glycosylation site (i.e., Ser, Thr, Asn, Gln in the case of a genetically encoded peptide) of the starting peptide.

With regard to the issue of "functions", we respectfully point out that many the instant claims, including 32, are to libraries per se. Hence, it is not necessary that the claimed libraries possess all of the disclosed functions. The only examined method of use claim was 38.

With regard to an antibody like function, we interpret that as meaning that the peptide specifically binds a target molecule. The experience with peptide libraries is that with

a sufficiently diverse libraries, one or more binding peptides can be found for any target of interest. Certainly, if the core peptide of our glycopeptide library binds a target of interest, there is a reasonable expectation that one or more of our glycopeptides will also bind that target.

That said, in our opinion the library members do not have to actually offer the desired function, merely be screenable for it. If the library does not contain any members with a desired function, then that tells the skilled worker to avoid those members, and perhaps also closely related molecules. Screening a combinatorial library allows one to quickly eliminate potential binding molecules which don't work.

Competitive inhibitory activity is also commonly encountered in peptide libraries. That is, there is a known target-binding ligand, one or more peptides will competitively inhibit the binding to the target.

It is reasonable to expect that if the core peptide has immunostimulatory activity, and the library is sufficiently diverse, one or more of the library members will possess at least some of that activity. If they don't, then if some of the members bind the active site, then by occluding the site so the core peptide cannot act, then they demonstrate a competitive inhibitory function.

We have amended method claim 38 to require screening merely for target binding (i.e., antibody-like) activity. When such binding activity, in vivo, has a biological effect, then one is in effect screening for a biological activity (see new claim 51). Immunostimulatory activity (new claim 52) is simply one form of biological activity. Binding, whether <u>in vivo</u> or <u>in vitro</u>, can competively inhibit a known ligand (new claims 53-54).

We again remind the Examiner that Appendices 1 and 2 demonstrate the general acceptance of combinatorial library

claims as satisfying description even though there is a random component.

5.2. We do appreciate the examiner's concession that there is description for a glycopeptide library derived from the MUC1 protein.

The Examiner's attention is respectfully directed to claims 49, 45 (III), 65, 67, 68, 69 and 72.

5.3. The Examiner also asserts that applicants have acquiesced in the description rejection relating to "adhesion ligands for bacterial receptors expressed on human cell surface antigens".

The claim erroneously referred to "adhesion ligands for bacterial receptors expressed on human cell surface antigens. The adhesins are bacterial proteins, and they bind to carbohydrate receptors expressed on human cell surface antigens (which may be glycolipids or glycoproteins). Claims 30 and 32 have been amended accordingly.

It is well known in the art that bacteria bind to mammalian cells, and that such binding is the result of the binding of bacterial proteins (adhesins) to cell surface receptors. Some of these receptors are carbohydrate in character.

A good review of adhesin-carbohydrate receptor interactions appears in Karlsson, et al., "Microbial Interaction with Animal Cell Surface Carbohydrates", APMIS Suppl. 27:71-83 (1992) (copy enclosed). According to Karlsson, the principal bacterial adhesin targets are

lactosylceramide (R1-Galβ4Glc-R2)
galabiose (R1-Galα4Gal-R2)
sialic acid (R1-NeuAC-R2).

Karlsson notes that E. coli class II adhesin binds to globoside (GalNAcβ3 Galα4Gal β4 Glc β Cer), and E. coli Class

III adhesin to Forssman glycolipid (GalNAc α3 GalNAc β3 Gal α4 Gal β4 Glc β cer) and to blood group A globoside (GalNAc α3 (Fucα2) Gal β3 Gal NAc β3 Gal α 4 Gal β4 Glc β Cer).

See also Beachey, "Bacterial adherence: adhesin-receptor interactions mediating the attachment of bacteria to mucosal surface", J. Infect. Dis. 143(3):325-45 (1981) and Feizi, "Glycoprotein oligosaccharides as recognition structures", Ciba Found. Symp. 145:62-79 (1989) (copies enclosed).

The component carbohydrate structures (i.e., the individual sugars) forming the carbohydrates receptors for bacterial adhesins are, not surprisingly, the same as those which are incorporated into cancer-associated mucins. Obviously, they are the typical sugars of mammalian glycoproteins: Gal, GalNAc, Glc, GlcNAc, Fuc, Sialic acid (NeuAc) and Man.

At the time of filing of provisional application 60/056,240 (1997), the art was well aware of the structural character of the adhesin receptors contemplated by claim 30, and patent law does not require specific identification of those receptors unless the receptors are expressly claimed.

6. Definiteness Issues

The Examiner asserts that the claims are indefinite because the identities of the compounds comprising the library are unknown, and that the identification is feasible by reference to a specific parent compound.

However, applicants plainly disclose that a variety of different parent compounds can be used – although, for any given library, there is just one parent compound.

Claim 32, as amended, recites that (1) there is only one peptide scaffold, (2) the scaffold comprises an O-linkable glycosylation site, and (3) the carbohydrate structure components are associated with human cancer mucins or with the

human cell surface carbohydrate receptors recognized by bacterial adhesins.

We again remind the Examiner that Appendices 1 and 2 demonstrate a consensus that claims to libraries are definite even though the recited molecules have a random element.

7. Objection

The examiner objects to the phrase "combinatorially-generated glycopeptide library". Combinatorial generation of a glycopeptide library is clearly disclosed at P5, L16-23.

8. Finality

On May 28, the Examiner advised Counsel that presentation of any claim not identical in scope to one already pending would be deemed to raise a new issue requiring further consideration and search. Since this amendment does present such claims, the next action cannot be made final.

Respectfully submitted,

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Enclosures
-Appendix 1
-Appendix 2
-Karlsson (1992)
-Beachey (1981)
-Feizi (1989)

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